REMARKS

Amendments are made to the pending claims. Claims now pending are still 42-53. A marked up version of the claims showing all changes is attached hereto.

The informalities of claims 43, 46, 48, 49, 51 and 52 have been corrected in accordance with the Examiner's suggestions.

Applicants have also accepted the Examiner's suggestion with respect to claim 44. However, applicants state that the subject matter of the original claim 44 does not read upon a product of nature, because such a combination of nucleic acids is not believed to exist in nature. However, applicants view the rejection as being in the nature of an informality, and have accepted the Examiner's suggestion.

Claim 54 has been added. It is supported by, *inter alia*, Example 3, original claim 9 and Seq. Id. Nos. 2-4 of the original application.

In paragraph 9, the Examiner has rejected claims 42, 50 and 53 under 35 U.S.C. § 112, 2d paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. The Examiner states that "because it is unclear from the instant specification if all nucleic acid molecules of plant origin encoding an EPSPS enzyme have threonine at amino acid position 102 and a proline at amino acid position 106, one of skill in the art would not know to which nucleic acid molecules the claims are directed and thus the metes and bounds of the claimed invention."

This rejection is respectfully traversed, because the invention is directed to mutating the coding sequences that normally encode a specific Thr and a specific Pro in the EPSPS sequence, and not to mutating a residue at a given numerical position. That is, the reference to positions 102 and 106 is not to identify a position to be mutated, but to simply to identify the relevant Thr and Pro that are mutated to Ile and Ser, respectively. The exact numerical numbering sequence of the two residues in the enzyme protein may change depending on the particular enzyme, as explained in detail *infra*. The application at page 3, lines 23-24 clearly states that the numerical numbering sequence is "relative to the gene from which it is derived."

E

Perhaps applicants' choice of language in the claims as filed led to this confusion, and, therefore, claims 42, 47, 50 and 53 have been amended to eliminate the ambiguity and to more clearly define the invention as a modified nucleic acid molecule of plant origin encoding an EPSPS enzyme, comprising: (1) a first modification of a coding sequence that normally encodes threonine that is located, relative to the gene from which it is derived, at position 102 of the amino acid sequence of mature EPSPS sequence of SEQ ID NOs: 3, to encode isoleucine in a mature plant EPSPS sequence; and (2) a second modification of a coding sequence that normally encodes proline that is located, relative to the gene from which it is derived, at position 106 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode serine in a mature plant EPSPS sequence. The language of the claims is completely supported by the application at the bottom of page 3 to the top of page 4.

An EPSPS enzyme in a plant will contain multiple Thr and Ser residues, and this application specifies the substitution of a specific Thr with Ile and a specific Pro with Ser, and that the references to "102" and "106" did not direct substitutions at those positions, but identified the specific Thr and Pro residues where the substitution occurs. This is further demonstrated by the Declaration of Dr. Rick DeRose, which is concurrently filed. As plainly stated by Dr. DeRose, a person of ordinary skill in the art will have recognized as of July 19, 1995 and recognizes that specific amino acid residues -- i.e., Thr and Pro -- are mutated, not "positions." DeRose Declaration, paragraph 26.

In paragraphs 10 and 11, the Examiner rejected claims 42, 47, 50 and 53 under 35 U.S.C. § 112, 2d paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention, because the phrase "of mature EPSPS sequence" is indefinite. The amendments to claims 42, 47, 50 and 53 are believed to have corrected any unclarity that may have existed.

In paragraph 12, the Examiner rejected claims 48, 49, 51 and 52 under 35 U.S.C. § 112, 2d paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention, because the phrase "increased

E

tolerance" is relative and does not state the metes and bounds of the claimed invention. The amendments to claims 48, 49, 51 and 52 are believe to have rendered moot that rejection.

In paragraph 14, the Examiner rejected claim 42 as follows:

> Claim 42 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, Applicant has only described a modified maize EPSPS encoding polynucleotide having the claimed modification. Applicant does not describe any other plant EPSPS encoding polynucleotides having the claimed modifications. Hence, it is unclear from the instant specification that Applicant was in possession of the invention as broadly claimed.
>
> See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism
>
> In addition, see *Fiers* 25 USPQ 2d (CAFC 1993) at 1606 that states "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it; what is required is a description of the DNA itself.".

Applicants respectfully traverse this rejection. Section 112 provides that a patent specification "shall contain a written description of the invention." 35 U.S.C. § 112, ¶ 1 (1994). To satisfy the written description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. See *Vas-Cath Inc. v. Mahurkar*, 935 F.3d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The written description does not require that every single embodiment of anything that would fall within the scope of the claims be specifically described, and *University of California v. Eli Lilly and Co.* does not stand for any

E

such proposition.

The Federal Circuit has repeatedly held that application of the written description requirement will necessarily vary depending on the nature of the invention claimed. As explained herein, the facts here are quite different from the facts in *Lilly* and a different level of written description is provided.

Unlike the facts in *Lilly*, the application here does not describe a gene material merely by a statement of function or result. *Lilly* stated that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." *Id.*, 43 USPQ2d at 1404 The Court also stated that a disclosure that allowed one skilled in the art to visualize or recognize the identity of the subject matter of the claim would meet the written description requirement. *Id.*, 43 USPQ2d at 1406.

The present application complies with this test, since the application describes the claimed sequences by more than their function, and properly and adequately characterizes the claimed invention. The invention here comprises two specific mutations in the residues of a plant EPSPS enzyme. The structure of the resulting, mutated plant EPSPS enzyme is thus clearly defined. It is any plant EPSPS enzyme sequence that has the two specific mutations -- that is a plant EPSPS enzyme that had a specific Thr residue (located at position 102 of the maize EPSPS sequence) substituted by Ile, and a specific Pro residue (located at position 106 of the maize EPSPS sequence) substituted by Ser. That completely describes the claimed invention, and it is not necessary that the inventors set out the entire sequence of each and every such EPSPS enzyme. As described in the DeRose Declaration, the EPSPS sequence of many plant EPSPS enzymes had already been published by the date of the instant application. Those sequences were known and available to a person of ordinary skill in the art. The Examiner in effect is suggesting that the applicants should have copied the published EPSPS sequences into this application with the two Thr and Pro residues modified to show the Ile and Ser. That requirement would not further the requirement to provide a full disclosure, but instead, would merely bulk up the

E

disclosure with unnecessary material. A person of ordinary skill in the art reading the application can visualize any plant EPSPS enzyme sequence with the two mutations, given the prior published EPSPS sequences.

In paragraph 15, the Examiner rejected claims 42, 45, 46 and 50-53 as follows:

> 15. Claims 42, 45, 46 and 50-53 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide of maize origin encoding a modified 5-enolpyruvylshikimate-3-phosphate synthase having the claimed modifications, vectors, transgenic plants and plant cells comprising said DNA sequence, and a method of protecting plants comprising said transgenic plants, does not reasonably provide enablement for all isolated polynucleotides of plant origin encoding a modified 5-enolpyruvyl-shikimate-3-phosphate synthase having the claimed modifications, vectors, transgenic plants and plant cells comprising said DNA sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is repeated for the reason of record as set forth in the last Office action mailed 14 June 2001. Applicant's arguments filed 16 October 2001 have been fully considered but they are not persuasive.
>
> Applicant argues that the specification states expressly that the modified DNA molecule may be of plant origin (page 4, lines 13-14 of the Remarks). Applicant argues that the domain of the EPSPS enzyme overlapping relative positions 102 to 106 (of the maize sequence) has been recognized in the prior art as being highly conserved in plants (page 4, lines 24-25 of the Remarks). In addition, Applicant argues that the prior art teaches that EPSPS enzymes in plant species have significant similarity, citing USP 5,310,667, figure la-b, and that it would not have required undue trial and error experimentation for one of ordinary skill in the art to isolate all DNA sequences encoding an EPSPS gene and modify them as claimed (pages 5-6 of the Remarks). The Examiner responds, that the statement of intent to modify other plant DNA molecules does not necessarily enable the specification within the scope of the instant claimed invention. It is noted that Applicant claims modification of an EPSPS enzyme at positions 102 and 106, not relative positions. In addition, Applicant's reliance upon the teachings of others directed to different mutations of the EPSPS enzyme is irrelevant. The '667 patent teaches modification of the petunia, tomato, *Brassica* and maize genes encoding the same modification and producing the same glyphosate tolerance. Applicant has only taught that modification at positions 102

E

and 106 of the maize EPSPS enzyme produces a glyphosate tolerant enzyme.

Applicants respectfully traverse this rejection.

First, the Examiner states that "It is noted that Applicant claims modification of an EPSPS enzyme at positions 102 and 106, not relative positions. ... Applicant has only taught that modification at positions 102 and 106 of the maize EPSPS enzyme produces a glyphosate tolerant enzyme." That is not correct. The application at page 3, lines 23-24 clearly states that the numerical numbering sequence is "relative to the gene from which it is derived." Further, as detailed in the DeRose Declaration at paragraph 26, any person skilled in the art reading the application in 1995 would have understood, and would understand today, that it is a particular residue that is being modified, not a "position."

Second, the application should be found to be enabling for what is claimed under controlling precedent. In *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988), the Court indicated that resolving an enablement inquiry involves consideration of certain factors: breadth of claims; nature of the invention; state of the prior art; level of skill in the art; level of predictability; amount of direction/guidance; presence/absence of working examples; and the quantity of experimentation. Further, in *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 56 U.S.P.Q.2d 1332 (Fed. Cir. October 3, 2000), the Court adopted a finding of the district court which is relevant here:

> Enablement is determined from the viewpoint of persons of skill in the field of the invention at the time the patent application was filed. ... Responding to ADM's argument that the claims could cover myriad bacterial strains not yet known, the court stated:
>
> > According to the record, all of the methods needed to practice the invention were well known to those skilled in the art. Despite the diversity existing among bacteria, practitioners of this art were prepared to carry out the identification, isolation, recombination, and transformation steps required to practice the full scope of the claims.

The "Wands factors" are discussed below.

E

Nature of the Invention and Breadth of Claims: The general nature of the invention is the obtaining of glyphosate tolerant EPSPS enzymes. The claims here are relatively narrow in that they cover a specific combination of two specific mutations in a mature plant EPSPS enzyme. The claims do not purport to cover all EPSPS enzymes or a broad range of mutations. The claims do not cover bacterial or yeast derived EPSPS. As will be further detailed below, the invention involves a fairly well-developed area of art.

State of the Prior Art: As evidenced by the cited prior art and as set forth in the DeRose Declaration, the state of the prior art with respect to EPSPS structure, its function in plants, decoding of the specific sequences, methods of mutating EPSPS, transformation of plants with EPSPS constructs to obtain glyphosate tolerance, and the like was fairly well-developed at the time the subject invention was made.

Level of Skill in the Art: The art is represented by the patentees of the many patents in this area, most of whom possess a Ph.D. and have years of experience in the art. The Examiner will also recognize from the many issued patents and applications in this art that, by 1995, the design of vectors for introducing glyphosate tolerance into plants, and plant transformation with such vectors, was essentially routine.

Level of Predictability: Prior to the subject invention , whether a given mutation or combination of mutations in an EPSPS sequence will provide glyphosate tolerance was arguably unpredictable. However, once certain mutations in a plant EPSPS were established to provide glyphosate tolerance while permitting the EPSPS to perform its normal catalytic function, it was relatively predictable that the same mutations in other plant EPSPS sequences would also work. Thus, as attested in the DeRose Declaration:

> 10. In fact, it was recognized in 1995, as it is today, that plant EPSPS enzymes are effectively interchangeable. Thus, one can eliminate or disable the EPSPS enzyme in a plant species, and substitute an EPSPS enzyme from another plant species, and the plant will function. This is demonstrated by the fact that, as shown in this application, as well as in many prior publications, an EPSPS enzyme from a first plant species mutated to be glyphosate tolerant can be introduced into a plant of a second different species than the first species, and yet

E

> the glyphosate will disable the wild-type or natural enzyme in the second species, but the plant will continue to function, because the mutated glyphosate-tolerant EPSPS enzyme of the first plant species continues to perform the normal EPSPS catalytic function in that plant. Even as of today, there has never been any report of a heterologous plant EPSPS enzyme that did not function in a plant of a different species in the same manner as the wild-type or natural EPSPS enzyme.
>
> 11. The plant EPSPS enzymes were viewed to be essentially interchangeable because all have the very highly conserved active site in the area of residue numbers of about 90 - 110 described above.

This is not to say, necessarily, that the EPSPS enzymes of all plants, mutated in accordance with the invention here, would work equally well, or that the specific choices of nucleotides in a vector would not have some effect. A possible difference of degree of effectiveness should not be found to negative the utility of the sequences.

Amount of Direction/Guidance and Presence/Absence of Working Examples: Given the straightforward nature of the invention in a well-developed art (as of 1995), and the art-recognized similarity of plant EPSPS sequences, the application, including the working example, provides sufficient guidance to make the claimed mutations in any plant EPSPS sequence.

Quantity of Experimentation: The law anticipates a reasonable amount of routine experimentation in order to practice a claimed invention. Patent law only requires that such experimentation must not be "undue." See, e.g., *Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'") The Examiner has not pointed to any basis for suggesting that any experimentation to apply the invention to other EPSPS genes or mature enzymes would be "undue." To the contrary, Applicants believe that such screening, while perhaps tedious, is more aptly described as "routine" in this art. It should be noted that screening for glyphosate tolerance can be carried out *in vitro* in cells and need not even involve growing of entire plants.

In summay, to paraphrase the *Ajinomoto* decision, *supra*, "all of the methods needed to

E

practice the invention were well known to those skilled in the art. Despite the diversity existing among [plants], practitioners of this art were prepared to carry out the identification, isolation, recombination, and transformation steps required to practice the full scope of the claims."

Based on the foregoing amendments, evidence and remarks, reconsideration of the rejections and favorable action on claims 42 to 54 is requested.

Respectfully submitted,

CONNOLLY BOVE LODGE & HUTZ LLP

By _____

Robert G. McMorrow, Jr.
Reg. No. 30,962
Tele. (302) 658-9141
1220 Market St.
Wilmington, DE 19899

Encl: 1. DECLARATION OF RICHARD T. DEROSE, PHD (with attachments)
2. Petition for Extension of Time, with fee

E

APPENDIX A

Version of Amended Claims with Markings to Show Changes Made.

42 (Amended). A modified nucleic acid molecule of plant origin encoding an EPSPS enzyme, the modifications comprising:

a first modification[, at the position which] of a coding sequence that normally encodes a threonine that is located, relative to the gene from which it is derived, at position 102 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode isoleucine in a mature plant EPSPS sequence; and

a second modification[, at the position which] of a coding sequence that normally encodes a proline that is located, relative to the gene from which it is derived, at position 106 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode serine in a mature plant EPSPS sequence.

43 (Amended). [A] The nucleic acid molecule as claimed in claim 42 wherein the modified nucleic acid molecule is of maize origin.

44 (Amended). [A nucleic acid] An isolated polynucleotide molecule having the sequence of SEQ ID NO: 4.

46 (Amended). [A] The vector of claim 45 further comprising nucleic acid encoding a chloroplast transit peptide operably associated with, and in the order of transcription between, the promoter functional in a plant cell and the nucleic acid of claim 42.

47 (Amended). A plant cell comprising a vector comprising the following components,

E

which are operably associated in the direction of transcription:

(a) a promoter functional in a plant cell;

(b) nucleic acid encoding a chloroplast transit peptide;

(c) a modified nucleic acid molecule of maize origin encoding an EPSPS enzyme, the modifications comprising:

a first modification[, at the position which] of a coding sequence that normally encodes a threonine that is located, relative to the gene from which it is derived, at position 102 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode isoleucine in a mature plant EPSPS sequence; and

a second modification[, at the position which] of a coding sequence that normally encodes a proline that is located, relative to the gene from which it is derived, at position 106 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode serine in a mature plant EPSPS sequence; and

(d) an untranslated transcription termination signal region.

48 (Amended). [A] The plant cell of claim 47 which is a monocot with increased tolerance to glyphosate herbicides relative to an unmodified plant cell.

49 (Amended). [A] The plant cell of claim 47 which is a dicot with increased tolerance to glyphosate herbicide relative to an unmodified plant cell s.

50 (Amended). A transgenic plant comprising a vector comprising the following components, which are operably associated in the direction of transcription:

E

(a) a promoter functional in a plant cell;

(b) nucleic acid encoding a chloroplast transit peptide;

(c) a modified nucleic acid molecule of plant origin encoding an EPSPS enzyme, the modifications comprising:

a first modification[, at the position which] of a coding sequence that normally encodes a threonine that is located, relative to the gene from which it is derived, at position 102 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode isoleucine in a mature plant EPSPS sequence; and

a second modification[, at the position which] of a coding sequence that normally encodes a proline that is located, relative to the gene from which it is derived, at position 106 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode serine in a mature plant EPSPS sequence; and

(d) an untranslated transcription termination signal region.

51 (Amended). [A] The transgenic plant of claim 50 which is a monocot with increased tolerance to glyphosate herbicides relative to an unmodified plant.

52 (Amended). [A] The transgenic plant of claim 50 which is a dicot with increased tolerance to glyphosate herbicides relative to an unmodified plant.

53 (Amended). A method for selectively controlling plants which method comprises the steps of:

a) planting crop seeds or plants which have increased glyphosate tolerance as a result of a

E

chimeric gene being inserted into said crop seed or plant, said chimeric gene having

(i) a promoter region functional in a plant cell; and

(ii) a nucleic acid molecule of plant origin encoding a modified EPSPS enzyme, the modifications comprising:

a first modification[, at the position which] of a coding sequence that normally encodes a threonine that is located, relative to the gene from which it is derived, at position 102 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode isoleucine in a mature plant EPSPS sequence; and

a second modification[, at the position which] of a coding sequence that normally encodes a proline that is located, relative to the gene from which it is derived, at position 106 of the amino acid sequence of mature EPSPS sequence of SEQ ID NO: 3, to encode serine in a mature plant EPSPS sequence; and

(iii) an untranslated transcription termination signal region; and

b) applying to said plants a sufficient amount of glyphosate to control said untransformed plants without significantly affecting said plants that comprise the chimeric gene.

::ODMA\MHODMA\CB;186957;1

E